

Higher Vitamin D Dietary Intake Is Associated With Lower Risk of Alzheimer's Disease: A 7-Year Follow-up

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Background. Hypovitaminosis D is associated with cognitive decline among older adults. The relationship between vitamin D intakes and cognitive decline is not well understood. Our objective was to determine whether the dietary intake of vitamin D was an independent predictor of the onset of dementia within 7 years among women aged 75 years and older.

Methods. Four hundred and ninety-eight community-dwelling women (mean, 79.8 ± 3.8 years) free of vitamin D supplements from the EPIDemiology of Osteoporosis Toulouse cohort study were divided into three groups according to the onset of dementia within 7 years (ie, no dementia, Alzheimer's disease [AD], or other dementias). Baseline vitamin D dietary intakes were estimated from self-administered food frequency questionnaire. Age, body mass index, initial cognitive performance, education level, physical activity, sun exposure, disability, number of chronic diseases, hypertension, depression, use of psychoactive drugs, and baseline season were considered as potential confounders.

Results. Women who developed AD ($n = 70$) had lower baseline vitamin D intakes (mean, 50.3 ± 19.3 µg/wk) than nondemented ($n = 361$; mean intake = 59.0 ± 29.9 µg/wk, $p = .027$) or those who developed other dementias ($n = 67$; mean intake = 63.6 ± 38.1 µg/wk, $p = .010$). There was no difference between other dementias and no dementia ($p = .247$). Baseline vitamin D dietary intakes were associated with the onset of AD (adjusted odds ratio = 0.99 [95% confidence interval = 0.98–0.99], $p = .041$) but not with other dementias ($p = .071$). Being in the highest quintile of vitamin D dietary intakes was associated with a lower risk of AD compared with the lower 4 quintiles combined (adjusted odds ratio = 0.23 [95% confidence interval = 0.08–0.67], $p = .007$).

Conclusions. Higher vitamin D dietary intake was associated with a lower risk of developing AD among older women.

Key Words: Vitamin D—Alzheimers—Diet—Dementia—Older adults.

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HYPOVITAMINOSIS D is common among older adults, affecting up to 90% of the elderly population (1). This is crucial in that results of epidemiological studies suggest that hypovitaminosis D is associated with cognitive function and Alzheimer's disease (AD) (2–7). From a physiological point of view, vitamin D is a steroid hormone that exhibits neurosteroid actions in the central nervous system (8–10), and it has been proposed that the chronic deficit of vitamin D neurotrophic, anti-inflammatory as well as antioxidant properties may partially explain neuronal degeneration and AD (10).

Correction of hypovitaminosis D may potentially protect older adults against cognitive decline. To date, no randomized placebo-controlled trial has explored yet the benefits of vitamin D supplementation to treat or prevent dementia (10). Prior

to planning such a resource-consuming supplementation trial, considering the contribution of exogenous vitamin D in the diet may provide useful information. We recently showed that the dietary intakes of vitamin D were directly associated with the global cognitive performance in 5,596 women from the EPIDemiology of Osteoporosis (EPIDOS) cohort (11). Our study was yet limited by its cross-sectional design that prevented establishing the temporal sequence of events. A longitudinal follow-up remained thus necessary to conclusively determine whether low vitamin D dietary intakes precede cognitive decline and the onset of dementia. We had the opportunity to examine this hypothesis in a subgroup of the EPIDOS cohort as the cognitive status of participants from one centre, Toulouse, was reassessed after 7 years of follow-up (12,13).

The objective of this work was to determine whether the dietary intake of vitamin D was an independent predictor of the onset of dementia (ie, AD or other dementias) among older women.

METHODS

Study Population

EPIDOS Study.—The EPIDOS Study was a French, large, observational, prospective multicenter cohort study designed to evaluate during a 4-year follow-up the risk factors for hip fractures among women aged 75 years and older. The sampling and data collection procedures have been described elsewhere in detail (14). In summary, from 1992 to 1994, 7,598 participants were recruited in five French cities from electoral lists (Amiens, Lyon, Montpellier, Paris, and Toulouse). Exclusion criteria included inability to walk independently, institutionalization, previous history of hip fracture or bilateral hip replacement, and inability to understand or answer the study questionnaires. All included study participants received at baseline a full medical examination by trained nurses in each local clinical center, which consisted of structured questionnaires, information about everyday dietary habits and chronic diseases, and a clinical examination. Medications and vitamin supplementation were reported by direct inquiry. Women were also asked to bring all the medication, including vitamin D supplements, they were regularly taking to the clinical centre.

Toulouse Cohort Study.—At the end of the EPIDOS 4-year study, all participants included in the centre of Toulouse were invited to take part in an additional 3-year follow-up study. The data collection procedures and flow diagram have been described elsewhere in detail (12). In summary, all women who had given informed consent were offered a consultation exactly 7 years after their inclusion. They were assessed either at home or at the Department of Internal Medicine and Clinical Geriatrics of Toulouse University Hospital. Initially, 1,462 women were included in the EPIDOS study in Toulouse. At the end of the 7-year follow-up, data on cognitive status (ie, no dementia, AD, or other types of dementia) were available for 714 women (48.8% of the initial cohort). Of the other 748 women whose cognitive status remained undetermined, 193 (25.8%) died during follow-up, 414 (54.7%) were lost to follow-up, and 141 (18.9%) withdrew from the follow-up study (12). To focus solely on the association of dietary intakes of vitamin D with cognitive function, women were also excluded from the present analysis when they had taken vitamin D supplements within the 18 months preceding the baseline assessment ($n = 111$). Finally, full clinical data were available for 498 women who met the inclusion criteria.

Dependent Variable: Cognitive status after seven years of follow-up

At the seventh year of follow-up, cognitive status was assessed during a single standardized interview using the Mini-Mental State Examination (15) and the Grober and Buschke (16). The diagnosis of dementia was established in a double-blind manner with the same standardized method of testing by a geriatrician and a neurologist from Toulouse University Hospital, France, who had expertise in dementia. This method has shown excellent interrater agreement, with a kappa score close to 1 (17). Clinical suspicion of dementia was diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, criteria (18). Probable or possible AD was diagnosed according to the criteria of the National Institute of Neurological and Communicative Disorders/Alzheimer's Disease and Related Disorders Association working group (19). Computed tomography reports or the images themselves, when available, were reviewed to rule out reversible causes of dementia or contribute to the diagnosis of dementia subtypes (ie, cortical and subcortical atrophy or infarcts, intracerebral lesions [tumors or hematomas], white matter lesions, and presence of enlarged ventricles). Participants were then classified into three groups: nondemented subjects (ND), AD, and other dementias (OD).

Explanatory variable: Weekly dietary intakes of vitamin D

The baseline vitamin D dietary intakes of all participants were estimated from a modified Fardellone self-administered food frequency questionnaire (20). The 21-question food frequency questionnaire included two seafood items (lean fish [fresh, canning, or frozen], fat fish [herring, anchovy, salmon, sardine, cod liver, mackerel]) and six dairy items (milk, cream and yoghurt desserts, cream cheese, baked cheese, soft cheese). Other questions inquired about eggs, fruits and vegetables, starchy foods, chocolate, drinking, and meat products that were used in the computation of vitamin D intake. The dietary intakes of vitamin D in $\mu\text{g}/\text{wk}$ were obtained by multiplying the content of individual food items by the frequency of consumption and summing over all items (to convert to international units per week, multiply by 40). Vitamin D content of individual food items was based on the CIQUAL Database, which is continually updated by the French food safety agency (21). This variable has already been used to address the cross-sectional association with global cognitive performance (11). Finally, dietary intakes of vitamin D were sorted in increasing order and categorized into quintiles to evaluate the highest (ie, fifth) quintile's ability to prevent the onset of AD within 7 years.

Potential confounders

The following confounders were measured at baseline assessment: age, body mass index (in kg/m^2), initial cognitive performance, education level, physical activity, sun exposure at midday, disability, number of chronic diseases,

hypertension, current depression, use of psychoactive drugs (ie, benzodiazepines, antidepressants, or antipsychotics), and season of assessment.

A specially trained nurse assessed baseline cognitive performance using Pfeiffer Short Portable Mental State Questionnaire (SPMSQ) (22). The SPMSQ proved to be a sensitive and specific screening test for dementia in community dwellers (22) and has already been used to explore the association between vitamin D and cognitive performance (11,23). It consists of a 10-item composite questionnaire with a score ranging from 0 to 10, with 10 representing the best performance. Women who obtained at least the Elementary School Recognition Certificate were considered to have a high education level compared with those who did not. Disability was defined as Lawton eight-item Instrumental Activities of Daily Living score ≤ 4 (11). Women were also asked whether they participated in a sport or physical leisure activity regularly (ie, at least 1 hour a week for at least the past month). Additionally, because skin generates vitamin D under the action of solar ultraviolet-B radiation (1) and because the daily maximum values of hourly average ultraviolet-B irradiance occur along midday hours (24), the direct exposure of at least face and hands to sunlight between 11 AM and 3 PM was sought by asking the following standardized question: "When weather is nice, do you stay more than 15 minutes exposed to the sun (face and hands uncovered) between 11 AM and 3 PM?" and was coded as a binary "Yes" versus "No" variable. Evaluation of chronic diseases (ie, hypertension, diabetes, dyslipidemia, coronary heart disease, chronic obstructive pulmonary disease, peripheral vascular disease, cancer, stroke, Parkinson's disease, and depression) was based on self-report. In particular, information about hypertension and depression were obtained from the standardized question: "Do you currently suffer from hypertension or depression?"

Statistical analysis

The participants' characteristics were summarized using means and standard deviations or frequencies and percentages, as appropriate. Normality of data distribution was checked using skewness-kurtosis test. First, we checked how the subjects included in data analysis differed from the EPIDOS Toulouse cohort participants who were lost to follow-up or not included. Between-group comparisons were performed using the independent samples *t* test or the chi-square test, as appropriate. Second, comparisons between participants separated into three groups based on cognitive status at 7 years (ie, ND, AD, or OD) were performed using the chi-square test or the oneway analysis of variance, as appropriate. Further post hoc analyses were performed using Fisher Least Significant Difference test. Third, two fully adjusted logistic regression models were used to examine the association of the baseline dietary intakes of vitamin D (independent variable) with the onset of AD during

the follow-up, and with the onset of OD (dependent variables), while taking baseline characteristics into account. Analyses were conducted separately for each model. Finally, univariate and multiple logistic regression models (ie, fully adjusted model and stepwise backward method) were used to examine the association between belonging to the highest quintile of vitamin D dietary intakes at baseline assessment (independent variable) and developing AD during the 7-year follow-up (dependent variable). *p* values less than .05 were considered significant. Statistical analyses were performed with the use of the STATA software (version 11.0; Stat Corp, College Station, TX).

Ethics

Women participating in the study were included after having given their written informed consent for research. The study was conducted in accordance with the ethical standards set forth in the Helsinki Declaration (1983). The study protocol was approved by the local Ethical Committee.

RESULTS

The women included in data analysis ($n = 498$) were significantly younger than the other participants of the EPIDOS Toulouse cohort, had a better SPMSQ score at baseline, were less often disabled, and practiced exercise more often, with more frequent sun exposure at midday (Table 1). There were no significant differences for the other clinical characteristics, especially regarding vitamin D dietary intakes. The mean baseline dietary intake of vitamin D was 58.41 ± 30.09 $\mu\text{g/wk}$ (range 2.53–205.54). Ninety-eight women (mean age 78.7 ± 3.4 years) were in the highest quintile of vitamin D dietary intakes (range 77.72–205.54 $\mu\text{g/wk}$; mean 104.38 ± 27.7 $\mu\text{g/wk}$).

As indicated in Table 2, 361 women (72.5%) were nondemented at the end of the follow-up, 70 (14.1%) presented with AD, and 67 (13.4%) with OD. Women who developed AD had lower baseline vitamin D intakes (mean, 50.3 ± 19.3 $\mu\text{g/wk}$) than nondemented (mean, 59.0 ± 29.9 $\mu\text{g/wk}$) or those who developed OD (mean, 63.6 ± 38.1 $\mu\text{g/wk}$). Women with ND were also younger and had better initial cognitive performance compared with AD and OD (Table 2). Finally, women who developed AD were more often disabled at baseline than those with ND and were less exposed to sun than those with ND or OD. There were no significant differences for the other clinical characteristics (Table 2).

Table 3 shows multiple logistic regressions for AD or OD, with dietary intakes of vitamin D and baseline characteristics as explanatory variables. Dietary intakes of vitamin D were inversely associated with AD (odds ratio [OR] = 0.99, 95% confidence interval [95% CI]: 0.98–0.99), but not with OD. Advance in age was directly associated with OD (OR = 1.11, 95% CI: 1.03–1.19), whereas the initial cognitive performance was inversely associated with AD (OR = 0.69, 95% CI: 0.57–0.84) and OD (adjusted OR = 0.79, 95%

Table 1. Baseline Characteristics of Subjects

	EPIDOS Toulouse Cohort (n = 1,462)	Studied Sample (n = 498)	p Value*
Age, mean \pm SD (y)	80.64 \pm 3.91	79.84 \pm 3.80	<.001
Body mass index, mean \pm SD (kg/m ²)	25.19 \pm 4.00	25.12 \pm 4.01	.721
Short Portable Mental State Questionnaire score, mean \pm SD (/10)	8.39 \pm 1.99	8.82 \pm 1.26	<.001
High education level, n (%)	110 (11.6)	64 (12.9)	.410
Disability, n (%)	50 (5.2)	11 (2.2)	.007
Regular physical activity, n (%)	326 (34.0)	215 (43.2)	.001
Sun exposure at midday, n (%)	335 (34.9)	225 (45.4)	<.001
Number of chronic diseases, mean \pm SD	4.25 \pm 1.61	4.24 \pm 1.78	.947
Hypertension, n (%)	458 (47.8)	236 (47.4)	.937
Depression, n (%)	133 (13.9)	57 (11.1)	.132
Use psychoactive drugs, n (%)	458 (47.5)	230 (46.2)	.737
Dietary vitamin D intakes, mean \pm SD (μ g/wk)	58.44 \pm 26.55	58.41 \pm 30.09	.989

Note. p value significant (ie, <.05) indicated in bold.

*Based on t test or chi-square test, as appropriate.

CI: 0.65–0.96), and sun exposure at midday was inversely associated with AD (adjusted OR = 0.46, 95% CI: 0.25–0.86; Table 3).

Fewer women presented with AD within the highest quintile of vitamin D dietary intakes compared with the lower 4 quintiles combined (4.1% vs 16.7%, respectively; $p = .001$). Table 4 reports the univariate and multiple logistic regressions between developing AD within 7 years and belonging to the highest quintile of vitamin D dietary intakes at baseline evaluation compared with the other 4 quintiles combined. Highest dietary intakes of vitamin D were associated with a lower risk of AD after the 7-year follow-up (unadjusted OR = 0.21, 95% CI: 0.08–0.60), even after adjustment for confounders (adjusted OR = 0.23, 95% CI: 0.08–0.69) and also in the stepwise backward model (adjusted OR = 0.23, 95% CI: 0.08–0.67; Table 4). Furthermore, initial cognitive performance and sun exposure at

midday were significantly associated with a lower risk of AD (Table 4).

DISCUSSION

The main finding of this prospectively followed cohort study of 498 older women initially free of vitamin D supplements was that the baseline dietary intake of vitamin D was inversely associated with the onset of AD within 7 years. The highest consumption of dietary vitamin D was associated with a decreased incidence of AD by 4.35 times. There was no association between the baseline dietary intakes of vitamin D and the onset of OD.

Only two previous cross-sectional studies have addressed the relationship between dietary vitamin D and cognitive performance. The first one highlighted a negative correlation between the 3-day dietary intakes of vitamin D and poor

Table 2. Baseline Characteristics and Comparison of the Participants (n = 498) Separated Into Three Groups Based on the Onset of Dementia Within 7 Years

	Onset of			p Value*			
	No Dementia (ND), n = 361	Alzheimer's Disease (AD), n = 70	Other Dementias (OD), n = 67	Overall	ND Versus AD	ND Versus OD	AD Versus OD
Age, mean \pm SD (years)	79.27 \pm 3.60	81.38 \pm 4.11	81.25 \pm 3.78	<.001	<.001	<.001	.841
Body mass index, mean \pm SD (kg/m ²)	25.22 \pm 4.01	24.73 \pm 3.69	24.99 \pm 4.39	.959			
Short Portable Mental State Questionnaire score, mean \pm SD (/10)	9.05 \pm 1.00	8.09 \pm 1.54	8.34 \pm 1.73	<.001	<.001	<.001	.212
High education level, n (%)	46 (12.8)	11 (15.7)	7 (10.4)	.652			
Disability, n (%)	3 (0.8)	6 (8.6)	2 (3.0)	<.001	<.001	.132	.163
Regular physical activity, n (%)	165 (45.7)	24 (34.3)	26 (38.8)	.156			
Sun exposure at midday, n (%)	178 (49.3)	18 (25.7)	30 (44.8)	<.001	<.001	.496	.019
Number of chronic diseases, mean \pm SD	4.17 \pm 1.53	4.40 \pm 1.55	4.45 \pm 2.92	.374			
Hypertension, n (%)	171 (47.4)	32 (45.7)	33 (49.3)	.917			
Depression, n (%)	39 (10.8)	10 (14.3)	8 (11.9)	.703			
Use psychoactive drugs, n (%)	161 (44.6)	38 (54.3)	31 (46.3)	.331			
Dietary vitamin D intakes, mean \pm SD (μ g/wk)	59.00 \pm 29.90	50.33 \pm 19.32	63.62 \pm 38.12	.027	.027	.247	.010

Notes: p value significant (ie, <.05) indicated in bold.

*Comparisons based on chi-square test or oneway analysis of variance, as appropriate; post hoc analyses performed using Fisher Least Significant Difference test.

Table 3. Logistic Regression Showing the Association Between the Dietary Vitamin D Intakes at Baseline (independent variable) and the Onset of Dementia Within 7 Years (dependent variable)* Adjusted for Participants' Baseline Characteristics† (*n* = 498)

	Type of Dementia*			
	Onset of Alzheimer's Disease		Onset of Other Dementias	
	Adjusted OR (95% CI)	<i>p</i> Value	Adjusted OR (95% CI)	<i>p</i> Value
Dietary vitamin D intakes (μg/wk)	0.99 (0.98–0.99)	.041	1.01 (1.00–1.02)	.071
Age	1.04 (0.97–1.12)	.251	1.11 (1.03–1.19)	.005
Body mass index	0.95 (0.88–1.03)	.223	1.01 (0.94–1.08)	.825
Short Portable Mental State Questionnaire score	0.69 (0.57–0.84)	<.001	0.79 (0.65–0.96)	.016
High education level	1.09 (0.50–2.37)	.839	0.78 (0.33–1.86)	.576
Disability	2.24 (0.57–8.86)	.249	0.50 (0.08–3.03)	.448
Regular physical activity	0.79 (0.44–1.42)	.433	0.83 (0.47–1.46)	.516
Sun exposure at midday	0.46 (0.25–0.86)	.015	1.19 (0.67–2.10)	.551
Number of chronic diseases	1.08 (0.91–1.28)	.373	1.05 (0.90–1.21)	.552
Hypertension	0.70 (0.38–1.29)	.256	1.01 (0.56–1.80)	.998
Depression	0.94 (0.40–2.19)	.877	0.99 (0.41–2.37)	.975
Use psychoactive drugs	1.18 (0.67–2.10)	.567	1.07 (0.61–1.86)	.823

Notes: CI = confidence interval; OR = odds ratio; odds ratio significant (ie, $p < .05$) indicated in bold.

*Two different regression models were used to predict the occurrence of Alzheimer's disease and other dementias.

†Including the influence of season at baseline, with no significant association with the onset of AD ($p = .350$) and OD ($p = .769$).

performance on Mini-Mental State Examination ($r = .35$, $p < .01$) among 69 community-dwelling elderly participants (25). The second study, by our team, showed among 5,596 community-dwelling older women free of vitamin D supplements from the EPIDOS study, that the weekly dietary intakes of vitamin D were cross-sectionally associated with the global cognitive performance measured with SPMSQ ($\beta = .002$, $p < .001$) (11). Our previous results additionally stressed that low weekly vitamin D dietary intakes were associated with cognitive impairment (OR = 1.30, $p = .024$) (11). Compared with the present study, both these works were cross-sectional, which precluded determining whether

cognitive decline precipitated low consumption of dietary vitamin D due to disability-induced undernutrition or whether low dietary intakes of vitamin D had a role in precipitating cognitive decline. To the best of our knowledge, the present study is the first one to use a prospective design, allowing us to conclude that the low consumption of vitamin D precedes the onset of AD, although eating lots of vitamin D rich foods is associated with a lower risk of developing AD.

AD is a neurodegenerative disease characterized by senile plaques consistent with extracellular accumulation of Aβ42 peptide and by hyperphosphorylation of TAU proteins that leads to neurofibrillary tangles (26). Taken together, these

Table 4. Univariate and Multiple Logistic Regressions Showing the Association Between Belonging to the Highest Quintile of Vitamin D Dietary Intakes at Baseline Assessment (independent variable) and Developing Alzheimer's Disease Within 7 Years (dependent variable), Adjusted for Participants' Baseline Characteristics* (*n* = 498)

	Onset of Alzheimer's Disease								
	Unadjusted Model			Fully Adjusted Model			Stepwise Backward Model		
	OR	95% CI	<i>p</i> Value	OR	95% CI	<i>p</i> Value	OR	95% CI	<i>p</i> Value
Highest quintile of vitamin D dietary intakes†	0.21	0.08–0.60	.003	0.23	0.08–0.69	.009	0.23	0.08–0.67	.007
Age	1.12	1.05–1.19	<.001	1.04	0.97–1.12	.291	—	—	—
Body mass index	0.97	0.91–1.04	.375	0.95	0.88–1.03	.221	—	—	—
Short Portable Mental State Questionnaire score	0.64	0.53–0.77	<.001	0.69	0.57–0.84	<.001	0.68	0.56–0.83	<.001
High education level	1.33	0.66–2.69	.433	0.99	0.46–2.20	.999	—	—	—
Disability	7.86	2.33–26.49	.001	2.48	0.63–9.80	.194	3.48	0.94–12.86	.061
Regular physical activity	0.65	0.38–1.10	.109	0.84	0.47–1.53	.576	—	—	—
Sun exposure at midday	0.36	0.21–0.64	<.001	0.45	0.24–0.85	.013	0.44	0.24–0.80	.007
Number of chronic diseases	1.06	0.93–1.20	.422	1.07	0.91–1.26	.421	—	—	—
Hypertension	0.91	0.55–1.51	.710	0.72	0.39–1.32	.289	—	—	—
Depression	1.40	0.67–2.93	.371	0.91	0.39–2.14	.831	—	—	—
Use psychoactive drugs	1.48	0.89–2.45	.133	1.16	0.65–2.06	.615	—	—	—

Notes: CI = confidence interval; OR = odds ratio; odds ratio significant (ie, $p < .05$) indicated in bold.

*Including the influence of season at baseline, with no significant effect ($p = .291$).

†Highest quintile versus lowest 4 quintiles combined.

lesions cause inflammation and oxidative stress involved in neuronal death as well as glutamate release with calcium neurotoxicity (26). Current preventive therapeutic strategies for AD primarily aim at fighting neuronal damages. Precisely, vitamin D has demonstrated neuroprotective effects that current antidementia drugs do not have (8–10). Experimentally, vitamin D reduces hippocampus degenerative processes in aging rodents and is involved in detoxification process by interacting with reactive oxygen and nitrogen species and by regulating the activity of γ -glutamyl transpeptidase (9). Neuronal survival may also result from vitamin D–related intraneuronal calcium homeostasis being maintained via the regulation of voltage-dependent calcium channels and via the synthesis of calcium-related cytoplasmic proteins such as parvalbumine or calbinding protein (8,10). In addition, vitamin D could also have an influential role in the amelioration of adverse effects in the amyloid hypothesis of AD because it may attenuate A β 42 accumulation by stimulating the innate immune system, specifically the phagocytosis and clearance of amyloid β -protein (10). Finally, experimentation reported that vitamin D supplementation in rodents resulted in an increase in choline acetyltransferase activity (thus an increase in acetylcholine availability) in several brain regions involved in memory (8).

Alongside vitamin D neurosteroid effects, the association of dietary intakes of vitamin D with AD may also be explained in a more general way by everyday dietary habits (26,27). In particular, there is reasonably good evidence that eating fish reduces the risk of dementia including AD (27–30). This effect is generally attributed to the omega-3 polyunsaturated fatty acids (27) even if data are conflicting. For instance, the Rotterdam Study, although having reported a 70% significant reduction in risk of AD after a 2-year follow-up with consumption of one fishmeal per week (28), failed to find an association between omega-3 fatty acids and the risk of AD after a 6-year follow-up (29). In addition, no clinical trial has shown yet a protective effect of fish oil supplements on cognitive decline (27). These mixed results strengthen the assumption that not only omega-3 acids but also another constituent of fatty fish—such as vitamin D—could prevent dementia (30). For illustration, women who did not develop dementia in our study consumed about 10 μ g/wk of vitamin D more than those who developed AD. In a practical sense, this corresponds to approximately 115 g (4 oz) of cooked salmon or cooked macquerel per week, or 170 g (6 oz) of tuna fish canned in oil (21,31). Also, the highest quintile of vitamin D dietary intakes, which was associated to a lower risk of developing AD within 7 years, corresponds to the consumption of about 50 mL of cod liver oil per week, or 100 g (3.5 oz) kipper fillet per day, or 200 g (7 oz) serving of sardines or anchovies canned in oil per day (21,31).

We failed to find a significant association between dietary vitamin D and the occurrence of non-AD dementias. At first sight, this seems to contradict previous literature proposing that vitamin D intakes could prevent vascular dementia

(32). Indeed, vitamin D neurotrophic action is neuroprotective in the case of cerebral ischemia (8), and hypovitaminosis D may be a vascular risk factor (33). It has been found among 318 older adults (mean age 74 years; 72.6% women) that subjects with hypovitaminosis D presented with more brain white matter hyperintensities ($p < .01$) and more vessel infarcts ($p < .01$) than controls (5). Inconsistencies with our study should be explained by the fact that non-AD dementias in our study could not be summed up with vascular dementias but also included neurosurgical or metabolic mechanisms that have no known relationship with vitamin D status.

Some limitations of this study need to be considered. First, the cohort was restricted to well-functioning women who might have easy access to vitamin D–rich foods and who might be unrepresentative of the general population of older adults. For instance, the mean dietary vitamin D intake of 58.4 ± 30.1 μ g/wk (range: 2.5–205.5) reported in our study was relatively high compared with previous studies reporting a mean intake around 40 μ g/wk in older adults with extremes values reaching 600 μ g/wk (34,35). Second, limitations of the study include the unavailability of a date of diagnosis of dementia and the lack of specific diagnosis of vascular dementia within the group of OD. Third, an additional limitation lied in the self-administration of the food frequency questionnaire that might expose cognitively impaired participants to provide unreliable and invalid dietary data (20). However, the exclusion of 74 women with cognitive impairment at baseline (ie, SPMSQ score < 8 (22)) did not alter the meaning and significance of our results (data not shown), revealing that the measure of vitamin D dietary intakes was robust. Fourth, the interpretation of our results should also account for the high percentage of lost to follow-up that reached one in two in our study. Finally, in order to provide complementary information to the growing number of studies examining the association of serum 25-hydroxyvitamin D (25(OH)D) concentration with cognitive function (2–7), we chose to examine instead the dietary intake of vitamin D, even if it is not the only contributor to 25(OH)D concentration. To limit confounding bias (36), we took into account other variables participating in 25(OH)D status such as sun exposure, season, body mass index, or age (1). However residual potential confounders, including the variables changes during follow-up, might still be present. Clinical trials are now warranted to explore the effect of vitamin D supplements on AD.

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CONFLICT OF INTEREST

All authors have no relevant financial interest in this manuscript. C.A. and O.B. served as unpaid consultants for Ipsen Pharma company in the past 3 years. Y.R. serves on a board for Cheisi, serves as a consultant for Lilly, Nutricia and Lundbeck, received grants from IDEM and Servier, and received payment for the development of educational presentations from Nutricia. B.V. serves on the board for the Fondation Plan Alzheimer, serves as a consultant for Astra-Zeneca, Danone/Nutricia, Eisai, Eli Lilly and Company, Exhonit, GlaxoSmithKline, Ipsen, Pfizer Inc, Roche and TauRx, and received grants from Avid Radiopharmaceuticals, Bristol Myers Squibb,

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